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Family History of Cancer and Risk of Lung Cancer in Lifetime Non-Smokers and Long-Term Ex-Smokers

ROSS C BROWNSON,* MICHAEL C R ALAVANJA, NEIL CAPORASO,** ERIC BERGER† AND JIAN C CHANG‡**

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Background. Genetic factors appear to play a role in the aetiology of lung cancer.

Methods. To examine the association between family history of cancer (all types) and risk of lung cancer among non-smokers, we conducted a case-control study. Cases (n = 618) were identified through the Missouri Cancer Registry for the period 1986 through 1991, and included 432 lifetime non-smokers and 186 ex-smokers who had stopped at least 15 years prior to diagnosis or had smoked for less than one pack-year. Controls (n = 1402) were selected through drivers licence and Medicare files.

Results. The risk of lung cancer increased directly in relation to the number of family members affected with cancer. The odds ratio (OR) associated with five or more first-degree relatives with cancer was 2.7 (95% confidence interval [CI] : 1.2–6.1), with a significant linear trend in risk according to the number of relatives affected ($P = 0.03$). Increased lung cancer risk was associated with two or more affected siblings (OR = 1.4; 95% CI : 1.0–1.9) and with two or more affected offspring (OR = 3.2; 95% CI : 1.3–8.1). Risk was slightly elevated for family history of lung cancer (OR = 1.3; 95% CI : 1.0–1.8).

Conclusions. Our study identified a slight increase in risk of lung cancer in relation to five or more relatives with cancer. Preventive implications of this increased risk are unclear because the attributable fraction is low in comparison to a variety of other factors.

Keywords: case-control study, genetics, lung neoplasms, tobacco smoke, women

Limited data from the US[1] and Italy[2] suggest that non-smoking lung cancer incidence is increasing. Lung cancer in non-smokers may account for more US deaths than any other cancer except colon and breast cancer in women and colon and prostate cancer in men.[3]

Despite its large public health impact, the aetiology of lung cancer among non-smokers is poorly defined. Established risk factors for lung cancer in non-smokers include exposure to environmental tobacco smoke[4] and a history of non-malignant lung disease.[5] Examples of less established risk factors for non-smoking lung cancer include saturated fat consumption,[6] residential radon exposure,[7–11] and occupational exposure to asbestos and pesticides.[12]

Although few studies have been conducted exclusively among non-smokers, genetic factors appear to play a role in the genesis of lung cancer. Tokuhata and Lilienfeld[13,14] first demonstrated familial clustering of lung cancer. Since these early reports, several additional studies[15–22] have shown a smoking-adjusted twofold to fourfold excess risk of lung cancer associated with a family history of cancer (primarily lung cancer). However, a recent cohort study of male twins showed no effect of inherited predisposition on lung cancer mortality.[23] Previous reports commonly have been limited by small numbers of non-smokers, lack of histological confirmation, and lack of adjustment for potential confounders, including family size.

Using a case-control method, we examined the association between family history of cancer and risk

* School of Public Health, Saint Louis University, 3663 Lindell Boulevard, St Louis, MO 63108-3342, USA.
** Division of Cancer Etiology, National Cancer Institute, Bethesda, MD, USA.
† Information Management Services, Rockville, MD, USA.
‡ Division of Chronic Disease Prevention and Health Promotion, Missouri Department of Health, Columbia, MO, USA.

of lung cancer among a large group of non-smoking women.

METHODS

Cases

Cases were identified through the Missouri Cancer Registry (MCR), which is maintained by the Missouri Department of Health. The Registry began collecting data on incident cancer cases from public and private hospitals in 1972, and hospital reporting was mandated by law in 1984. The MCR reporting procedures have been discussed in more detail elsewhere.[24] Of interest to this study, smoking history is reported to MCR via medical records, with previously documented accuracy of 83%.[24] To ensure complete reporting of female lung cancer cases for the current study, MCR staff completed special case ascertainment visits to participating hospitals. The case series included white Missouri women, aged 30–84 years, who were diagnosed with primary lung cancer between January 1986 and June 1991. Selection was limited to whites due to small numbers of other racial/ethnic groups. The case group included both lifetime non-smokers and ex-smokers who had stopped smoking $\geqslant$15 years prior to diagnosis or had smoked less than one pack-year (designated as 'non-smokers' in following sections). Ex-smokers of $\geqslant$15 years since cessation were included in the case group because the lung cancer risk due to smoking would be near baseline. Of the 3475 cases of female lung cancer reported for the study period, a total of 650 eligible cases was identified. Among these, physicians denied interview permission for 4% (n = 24) and an additional 1% (n = 8) refused to be interviewed. The final case group included 70% (n = 432) lifetime non-smokers and 30% (n = 186) ex-smokers. Of the 618 case interviews, 216 were conducted with cases themselves, and 402 were conducted with surrogates because the case was too ill to be interviewed or was deceased.

Histological Confirmation of Cases

In addition to the MCR-reported diagnosis of lung cancer case status, tissue slides were reviewed for histological verification for 76% (n = 468) of the cases. Slides for these cases examined simultaneously by three pathologists (TL, EI, and JM) using a multi-headed microscope without knowledge of the referring pathologist's diagnosis. In surgical specimens, consensus diagnoses were obtained with the criteria outlined in the World Health Organization classification scheme.[25] When only cytological material was available, consensus was obtained with standard cytological criteria.[26] Additional details on the procedures and results of histological verification are reported elsewhere.[27]

Controls

A population-based sample of white, non-smoking controls was ascertained by two methods. For women aged $<$65, a sample of state drivers licence files was provided by the Missouri Department of Revenue. Among the eligible cases aged $<$65, over 90% had a valid Missouri drivers licence at the time of the interview, suggesting the use of drivers licence files for control selection is appropriate. Among women aged 65–84 years, controls were generated from the Health Care Finance Administration's roster of Medicare recipients.[28] The Health Care Finance Administration enrollees are estimated to cover 95% of the women of the age group studied.[29] Based on the age distribution of lung cancer cases previously reported to the Registry, controls were age group-matched to cases. All controls were interviewed directly and the same definition of 'non-smokers' applied to controls as to cases. Among potentially eligible controls, 18% (n = 338) refused the initial screening interview and 7% (n = 122) of those screened eligible refused the full interview. The final control group numbered 1402.

Questionnaire Design and Administration

Telephone interviews were conducted by trained interviewers. The first phase of the interview consisted of a screening questionnaire to verify the age, race, and smoking status of cases and controls. For subjects who screened eligible and agreed to the full interview, the study questionnaire consisted of sections on residential history, passive smoke exposure, personal health history, family health history, reproductive history, occupational exposures, and dietary factors. Details on questionnaire sections for several risk factors have been described earlier.[5,6,11,12,30] The diet questionnaire was a 60-item, self-administered instrument.

Questions regarding family history of cancer focused on cancers among first-degree relatives (i.e. parents, full siblings, offspring). The interview ascertained type of relative and type of cancer. Information on family history of cancer was limited to first-degree relatives to minimize the length and complexity of the interview, and due to the previously reported[32,33] inaccuracy of reported cancers among second- and third-degree relatives.

Analyses

Odds ratios (OR) and 95% confidence intervals (CI) were calculated using multiple logistic regression,[34] adjusting for age, family size, and relatives' smoking history in all analyses. Others[35] have noted the importance

of adjusting for age and family size. The linearity of trends in risk according to number of relatives affected by cancer was evaluated with Mantel's one-tailed test.[36] We examined numerous potential confounding factors that have previously been reported as risk factors in this data set.[5,6,11,12,30] These included active smoking (i.e. for ex-smokers, personal smoking history), passive smoking, household radon exposure, saturated fat intake, occupation, and history of previous non-malignant lung diseases (e.g. pneumonia, tuberculosis, asthma).

RESULTS

Cases and controls were comparable in that most women in each group were >65 years of age, had at least a high school education, were married at some time in their lifetime, and were lifetime non-smokers (Table 1). Among the 402 surrogate case interviews, main respondents included a daughter or son, non-resident with the study subject (43%); spouse, resident with the subject (26%); sibling, non-resident with the subject (11%); other next of kin, resident with the subject (6%); and other relative, non-resident with the subject (14%).

Risk was only slightly elevated for women with one or more family members with cancer (all types) (OR = 1.1; 95% CI : 0.9–1.3). However, the risk of lung cancer increased directly in relation to the number of family members affected by cancer (all types) (Table 2). The OR associated with five or more first-degree relatives with cancer was 2.7 (95% CI : 1.2–6.1), with a significant linear trend in risk according to the number of relatives affected ($P = 0.03$). Odds ratios were generally larger among former smokers than among lifetime non-smokers. When surrogate interviews were excluded from the analyses, the OR were generally smaller than those presented in Table 2. Although sample sizes were insufficient for analyses by detailed cell type, OR were generally larger for non-adenocarcinomas (n = 280) than for adenocarcinomas (n = 255).

We examined lung cancer risk according to the type of first-degree relative affected (Table 3). Increased

TABLE 1 *Sociodemographic, smoking, and interview characteristics of lung cancer cases and controls, Missouri, 1986–1991*

Characteristic	Cases (n = 618)		Controls (n = 1402)	
	No.	%	No.	%
Age at interview (years)				
<55	46	7	103	7
55–64	85	14	233	17
65–74	193	31	457	33
75+	294	48	609	43
Education (years)				
<12	240	39	536	38
12	228	37	477	34
>12	121	19	355	25
Unknown/refused	29	5	34	3
Marital status				
Married	292	47	752	54
Widowed	269	44	537	38
Separated/divorced	31	5	65	5
Never married	26	4	47	3
Unknown	0		1	0
Smoking history				
Never smoker	432	70	1168	83
Former smoker	186	30	234	17

TABLE 2 *Odds ratios[a] (OR) for developing lung cancer according to number of first-degree family members with cancer (all types), Missouri, 1986–1991*

No. of family members affected	All subjects			Lifetime non-smokers			Former smokers		
	Cases/ controls	OR	95% CI	Cases/ controls	OR	95% CI	Cases/ controls	OR	95% CI
0	241/622	1.0		176/508	1.0		65/114	1.0	
1	185/475	1.0	0.8–1.3	139/396	1.0	0.8–1.3	46/79	0.9	0.6–1.5
2	93/197	1.2	0.9–1.6	72/171	1.2	0.9–1.6	21/26	1.3	0.8–2.6
3	31/69	1.1	0.6–1.7	25/60	1.1	0.7–1.9	6/9	0.9	0.3–3.0
4	15/23	1.6	0.8–3.2	9/22	1.1	0.5–2.5	6/1	9.8	1.1–86.2
⩾5	13/12	2.7	1.2–6.1	11/11	2.6	1.1–6.2	2/1	3.9	0.3–47.1
Trend (*P*-value)		(0.026)			(0.087)			(0.101)	

[a] Adjusted for age, family size, and pack-years of smoking.

TABLE 3 *Odds ratios[a] (OR) for developing lung cancer according to type of first-degree family member with cancer (all types), Missouri, 1986–1991*

Type and no. of family members	All subjects			Lifetime non-smokers			Former smokers		
	Cases/ controls	OR	95% CI	Cases/ controls	OR	95% CI	Cases/ controls	OR	95% CI
No. of parents affected									
0	417/979	1.0		309/811	1.0		138/168	1.0	
1	138/375	0.9	0.7–1.1	103/319	0.9	0.7–1.2	35/56	1.0	0.6–1.7
2	23/44	1.3	0.7–2.1	20/38	1.4	0.8–2.5	3/6	0.8	0.2–3.3
Trend (*P*-value)		(0.947)			(0.917)			(0.950)	
No. of siblings affected									
0	362/937	1.0		268/771	1.0		94/166	1.0	
1	133/318	1.0	0.8–1.3	103/265	1.1	0.8–1.4	30/53	9.0	0.5–1.5
⩾2	83/143	1.4	1.0–1.9	61/132	1.2	0.8–1.7	22/11	3.0	1.3–7.1
Trend (*P*-value)		(0.091)			(0.280)			(0.077)	
No. of offspring									
0	524/1297	1.0		390/1082	1.0		134/215	1.0	
1	43/93	1.1	0.8–1.7	34/80	1.1	0.7–1.7	9/13	1.2	0.5–3.1
⩾2	11/8	3.0	1.2–8.1	8/6	3.4	1.2–10.0	3/2	1.9	0.3–13.1
Trend (*P*-value)		(0.060)			(0.085)			(0.444)	

[a] OR for parents adjusted for age and pack-years of smoking; OR for siblings and offspring adjusted for age, family size, and pack-years of smoking.

lung cancer risk was associated with two or more affected siblings (OR = 1.4; 95% CI : 1.0–1.9) and with two or more affected offspring (OR = 3.2; 95% CI : 1.3–8.1).

Table 4 presents the risk of lung cancer according to the type of cancer in first-degree relatives. Risk was slightly elevated for lung cancer (OR = 1.3; 95% CI : 1.0–1.8). The elevated risk was primarily in the former smoker subgroup (lung cancer OR = 2.9).

Because lung cancer in non-smokers appears to be associated with a composite of relatively weak risk factors,[5,6,11,12,30] we examined risk while adjusting for a series of potential confounders (Table 5). After adjustment for age, family size, and a series of five previously identified risk factors, risk associated with cancer in five or more first-degree relatives remained elevated, with OR ranging from 2.2 to 2.7.

DISCUSSION

Our study allowed examination of lung cancer risk in relation to cancer in first-degree relatives in a group of non-smokers, free of the confounding effects of active cigarette smoking. We were also able to examine risk after adjustment for a variety of weak risk factors such as passive smoking and residential radon exposure. No published studies of family history of cancer and lung cancer risk have been conducted exclusively among non-smokers. Therefore, we will compare our findings with earlier studies of predominantly smokers.

Although we identified a trend in increasing risk according to number of first-degree relatives with cancer, only when five or more relatives were affected was the OR greater than two. Case-control data from the Texas Gulf Coast region showed an OR of 1.5 associated with four or more relatives with cancer.[22] Ooi *et al*.[16] found that a family history of two or more lung cancers was associated with an excess risk of 3.5; a lung cancer risk of 2.6 was associated with a family history of three or more non-lung cancers. In contrast to earlier case-control studies, a recent cohort analysis of male twins[23] showed little evidence of an inherited component for lung cancer.

We identified excess lung cancer risk for two or more siblings or offspring affected by cancer (all types). These findings vary from those of Shaw *et al*.[22] who found a

TABLE 4 *Odds ratios[a] (OR) for developing lung cancer according to type of cancer in first-degree family members, Missouri, 1986–1991*

Type of cancer (ICD-9 code)/ no. of relatives	All subjects			Lifetime non-smokers			Former smokers		
	Cases/ controls	OR	95% CI	Cases/ controls	OR	95% CI	Cases/ controls	OR	95% CI
Oral cavity (140–149)									
0	557/1362	1.0		418/1137	1.0		139/225	1.0	
⩾1	21/36	1.3	0.7–2.3	14/31	1.2	0.6–2.3	7.5	1.6	0.5–5.8
Stomach (151)									
0	550/1329	1.0		410/1111	1.0		140/218	1.0	
⩾1	28/69	0.9	0.6–1.5	22/57	1.0	0.6–1.7	6/12	0.6	0.2–1.8
Colon and rectum (153, 159, or 154 ex. 154.3)									
0	516/1270	1.0		379/1054	1.0		176/220	1.0	
⩾1	62/128	1.2	0.9–1.7	53/114	1.2	0.9–1.8	9/14	0.9	0.4–2.3
Liver (155)									
0	552/1348	1.0		411/1121	1.0		141/227	1.0	
⩾1	26/50	1.2	0.7–2.0	21/47	1.2	0.7–2.0	5/3	1.7	0.4–8.1
Lung (162)									
0	500/1259	1.0		381/1044	1.0		119/215	1.0	
⩾1	78/139	1.3	1.0–1.8	51/124	1.1	0.8–1.5	27/15	2.9	1.4–6.0
Breast (174)									
0	508/1236	1.0		378/1030	1.0		166/210	1.0	
⩾1	70/162	1.0	0.8–1.4	54/138	1.0	0.8–1.5	20/24	1.0	0.6–2.0
Uterus—unspecified (179)									
0	559/1340	1.0		414/1123	1.0		145/217	1.0	
⩾1	19/58	0.8	0.5–1.3	18/45	1.0	0.6–1.8	1/13	0.1	0.0–0.9
Uterine cervix (180)									
0	565/1379	1.0		422/1155	1.0		143/224	1.0	
⩾1	13/19	1.7	0.8–3.5	10/13	2.1	0.9–4.9	3/6	1.0	0.2–3.9
Prostate (185)									
0	548/1325	1.0		407/1105	1.0		141/220	1.0	
⩾1	30/73	1.0	0.6–1.6	25/63	1.1	0.7–1.7	5/10	0.8	0.3–2.5
Bladder (188)									
0	574/1385	1.0		429/1158	1.0		145/227	1.0	
⩾1	4/13	0.7	0.2–2.1	3/10	0.8	0.2–2.8	1/3	0.4	0.0–4.6
Non-Hodgkin's lymphoma (200, 202)									
0	566/1374	1.0		422/1148	1.0		144/226	1.0	
⩾1	12/24	1.3	0.6–2.7	10/20	1.4	0.7–3.1	2/4	0.8	0.1–4.8
Leukaemia (204–208)									
0	563/1338	1.0		422/1116	1.0		141/222	1.0	
⩾1	15/60	0.5	0.3–1.0	10/52	0.5	0.2–1.0	5/8	0.9	0.3–3.0

[a] Adjusted for age, family size, and pack-years of smoking.

TABLE 5 *Odds ratios for developing lung cancer according to number of first-degree family members with cancer (all types) after adjustment for potential confounding factors, Missouri, 1986–1991*

Adjusted for age, family size, relatives' smoking history and:	No. of family members affected					Trend (*P*-value)
	1[a]	2	3	4	5	
Active smoking (pack-years)	1.0 (0.8–1.3)	1.2 (0.9–1.6)	1.1 (0.7–1.7)	1.6 (0.8–3.2)	2.7 (1.2–6.1)	(0.025)
Passive smoking (spousal pack-years)	1.0 (0.8–1.2)	1.1 (0.8–1.5)	1.1 (0.7–1.7)	1.5 (0.8–3.0)	2.2 (1.0–5.1)	(0.098)
Household radon exposure (average 25-year—quartiles)	0.9 (0.7–1.2)	1.2 (0.9–1.6)	1.0 (0.6–1.7)	1.4 (0.7–2.8)	2.3 (1.0–5.7)	(0.116)
Saturated fat intake (average daily—quintiles[b])	1.0 (0.8–1.3)	1.3 (0.9–1.9)	1.2 (0.7–2.0)	1.5 (0.7–3.5)	2.7 (1.0–7.1)	(0.027)
Occupation[c]	1.0 (0.8–1.3)	1.2 (0.9–1.6)	1.1 (0.7–1.7)	1.6 (0.8–3.2)	2.4 (1.0–5.4)	(0.035)
Previous lung disease (dichotomous)	1.0 (0.8–1.2)	1.2 (0.9–1.6)	1.1 (0.7–1.7)	1.5 (0.8–3.0)	2.5 (1.1–5.7)	(0.040)

[a] Odds ratio (95% confidence interval).
[b] Quartile and quintile cutpoints were derived by equal divisions of the control sample.
[c] Exposure to asbestos, pesticides, and dry cleaning.

slight increase in lung cancer risk associated with having a mother with any cancer but no excess risk due to cancer among siblings or offspring. These differences may not be unexpected given that the Texas study contained a total of only 57 non-smoking cases and more males than females. A larger risk among offspring relative to siblings is not consistent with a genetic model of inheritance.[37]

In our analyses of lung cancer risk according to type of cancer in first-degree relative, elevations were noted for lung cancer and oral cavity cancer (in former smokers only). Elevated risk in association with family history of lung cancer is consistent with most earlier studies of smokers.[13–22] The increased odds of cancers of the lung and oral cavity seen in our study among former smokers also suggests the possibility of interaction between genetic susceptibility and smoking. Although based on small numbers, family history of uterine cancer decreased risk of lung cancer among former smokers.

To help explain the biological basis for epidemiological findings, three general categories of genetic host susceptibility factors are linked with lung cancer. The first is phase 1 p450 enzymes that likely act by enhancing (oxidative) activation of carcinogens in tobacco smoke.[38–40] A second group is based on differential ability to detoxify carcinogens, represented by glutathione-S-transferase. There is limited evidence for an association of deficient activity of this enzyme and both lung and bladder cancer.[41,42] Finally, there is a miscellaneous group of genes with diverse mechanisms (oncogene polymorphisms, nutrient metabolism, or unknown such as blood group polymorphisms). When present, associations have been weak and inconsistent, although evidence for excess H-ras vtr rare alleles in a variety of tumours (including lung cancer) has recently been presented.[43] While the interpretation of these genetic studies will remain complex, technical advances (i.e. polymerase chain reaction (PCR) methods to assay nanogram quantities of DNA and non-invasive approaches to obtaining DNA) are rendering large studies in populations more feasible. Opportunities to integrate these markers into well-designed field studies should increase.

Our study has several major strengths. These include the large sample size—one of the largest series of non-smoking lung cancer cases to date. In addition, we had relatively high response rates from both cases and controls. Finally, we conducted a pathology review of 76% of cases.[27]

A main limitation of our study is the possibility of recall bias that may affect the accuracy of reported family history of cancer. Although we have no direct information on the accuracy of reported family history of cancer from our data set, a related study[32] from Wisconsin found a high concordance between patient reports and medical records for cancer among first-degree relatives. Ignoring primary site, Love *et al*.[33] found 97% accuracy in reported cancer among first-degree relatives. In 83% of reported cancers in first-degree relatives, the primary site was correctly identified. Perhaps more important than concordance between case interview data and medical records is the potential bias of surrogate data for 65% of cases in our study. There is a possibility of detection bias, particularly for relatives' lung cancer among case families. We also conducted multiple comparisons, which raises the possibility of false positive associations. As noted in the work of Khoury and Flanders,[44] positive family history tends to overestimate relative risk and therefore, comparisons across case-control studies must be made with caution.

In summary, our study identified a slight increase in risk of non-smoking lung cancer in relation to five or more relatives with cancer. Preventive implications of this increased risk are unclear because the attributable fraction is low in comparison to a variety of other factors such as previous lung disease, diet, and environmental tobacco smoke.[45]

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